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Research under the direction of PD. Dr. W. Hess

Dilatation of the Choledochoduodenal Sphincter Induced by Chlorpromazine

Inaugural-Dissertation

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Introduction

Chlorpromazine, also known as Thorazine and Largactil, is 10-(gamma-dimethylaminopropyl)-2-chlorophenothiazine, a whitish-gray, photosensitive, water soluble powder [1]. It was first synthesized in France in 1951, and has since been widely accepted as a therapeutic in many branches of the medical profession.

Pharmacologically it acts on the central nervous system, predominantly on the hypothalamus, the reticular substance and the chemoreceptor trigger zone, as well as on the neurovegetative nervous system [1, 2].

Therapeutically it serves to potentiate anesthetics, narcotics and sedatives, in various psychiatric and neurological disorders, in the management of severe pain, as an antimetic, in the control of hiccoughs, to relieve bronchial asthma, in dermatological conditions having an emotional component, as an antipyretic, and in hypertension [1, 2, 3].

Numerous untoward effects have been described after chlorpromazine administration including drowsiness, dryness of the mouth, nasal congestion, epigastric discomfort, nausea, changes in bowel habits, urinary frequency, hypothermia, hypotension, tachycardia, extra-pyramidal symptoms, dermatological reactions, agranulocytosis, and jaundice [1, 2, 3].

Since the end of 1952 more than sixty articles presenting cases of chlorpromazine jaundice have appeared in medical literature throughout the world. In the majority of the cases reported a typical clinical picture, biochemical analysis, and histopathological finding consistently reappears. Usually jaundice is demonstrable between two and four weeks after chlorpromazine therapy has been instituted. The clinical picture may then include anorexia, malaise, abdominal distress, nausea, vomiting, constipation or diarrhea, clay colored stools, dark urine, and pruritis. Examination frequently shows the liver to be palpably enlarged, and usually tenderness in the right upper quadrant of the abdomen is present.

Laboratory test results show that the serum bilirubin, the serum total cholesterol and the alkaline phosphatase values are elevated, thus indicating that a retentional phenomenon exists.

Liver biopsy will then insure the diagnosis, and confirm that an obstructive jaundice with cholestasis in the biliary canaliculi is present.

These observations prompted investigators to consider the possibility that chlorpromazine might have an effect upon the tonus of the choledochoduodenal sphincter. *Menguy, Bollman, Grindlay and Cain* at the Mayo Clinic concluded after research on dogs that chlorpromazine in doses of 10 mg. per kilogram body weight does produce some biliary stasis by increasing resistance at the sphincter of Oddi [4].

The conclusion that was drawn urged further study and therefore we attempted to reproduce these findings on the choledochoduodenal sphincter in four dogs, as well as in man. Using similar but not identical techniques, we found that we were unable to reproduce the results obtained by the aforementioned investigators. Our study, demonstrated that chlorpromazine dilates the sphincter and reduces the intraductal pressure in man and tends to have the same effect in dogs.

Materials and Methods

The four dogs that were used all underwent cholecystectomy. Following excision of the gall-bladder, a polyethylene tube was introduced into the stump of the cystic duct and placed in the common duct with the open tip of the tube resting directly above the sphincter. The distal end of the tube was extended through the peritoneal cavity, secured with a mobilized segment of the greater

omentum, and passed through the abdominal wall to the surface of the abdomen.

The manometer that was used was patterned after the one described by Caroli. It is depicted in fig. 1. Tube C, drawing physiological

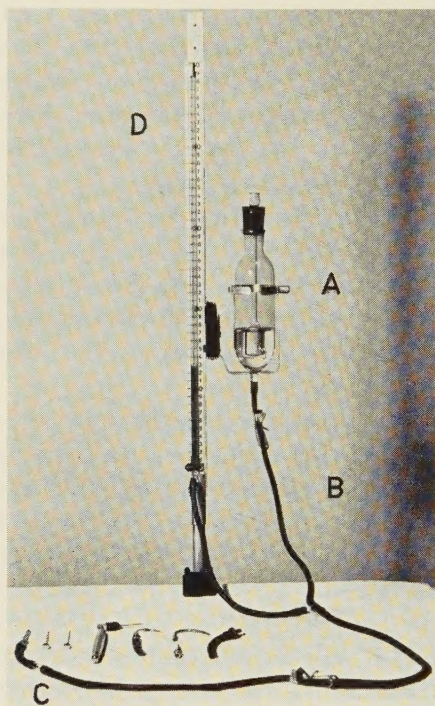


Fig. 1

saline solution from the reservoir in A, was connected to the presenting distal end of the polyethylene tube. Manometric zero was established at the level of the biliary sphincter with the dog lying prone. Resistance at the sphincter was measured by perfusing the solution through the system, with the clamps on tubes B and C open, at a pressure slightly exceeding the resistance at the sphincter. This was accomplished by raising the level of the reservoir (A) to a pressure which just permitted passage of the solution into the duodenum. The value recorded we refer to as the passage pressure. Immediately thereafter the clamp on tube B was closed permitting the observer to record the residual pressure at the sphincter.

Pressure readings taken before the administration of chlorpromazine showed that minor deviations must be expected depending on the tonus of the sphincter at any given moment. However, any significant deviations observed after injection of the drug we attribute to its action on the sphincter.

It is our opinion that measurement of the passage pressure and residual pressure in the described manner was physiologically sound. The biliary duct and sphincter were not stimulated more than once every five to ten minutes, when readings were taken, thus reducing the possibility that false values would be obtained through overstimulation.

Of the four dogs tested, two received 50 mg. of chlorpromazine intramuscularly, and two were given 10 mg. per kilogram intravenously (170 mg. and 240 mg. respectively).

On human subjects the investigative methods were essentially the same as those used on dogs. The group was comprised of ten cholecystectomized patients, and one patient with a cholecystostomy. These were in-patients of the Department of Surgery, Bürgerspital, Basle. Cholecystopathy was the indication for surgical intervention in each of the patients. Requirements for the testing procedure were fulfilled when during the course of the individual operations it was established that the common duct was without pathological lesion, that the sphincter was normal, and that when placing a T-drain in the common duct and taking pressure readings it could be demonstrated that a normotensive intraductal pressure and sphincter resistance existed. This T-drain was then left in place and approximately one week after surgery manometric readings before and after intramuscular injection of a standard dose of 25 mg. of chlorpromazine were taken with the Caroli apparatus and method.

Four of the eleven patients, at the time of testing, were also given 10 mg. of morphine intramuscularly. With the first of these four it was done to confirm the fact that morphine causes a rise in pressure by inducing a sphincter spasm [5]. Intramuscularly applied morphine will cause a rise in pressure within ten minutes and uphold a spasm up to two hours. Since it was observed at the onset of the testing with the three remaining patients that hypotensive conditions existed at the sphincter, the drug was used to induce a spasm which chlorpromazine then counteracted. We take this as further evidence of the dilatory action of chlorpromazine.

Results

Dogs

Dog I (fig. 2). This dog weighing 16 kg. displayed pressure values of a hypertensive nature at the onset of testing. These values then tended to approach a normal range but rose slightly again without apparent cause. At the end of the first hour of test readings 50 mg. of chlorpromazine were injected intramuscularly. Twenty minutes thereafter dilation of the sphincter was demonstrable. The decrease in resistance continued for a short period of time and when pressures tended to increase again, the test was concluded.

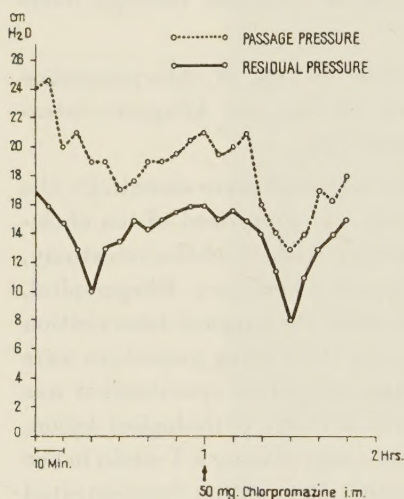


Fig. 2. Dog I.

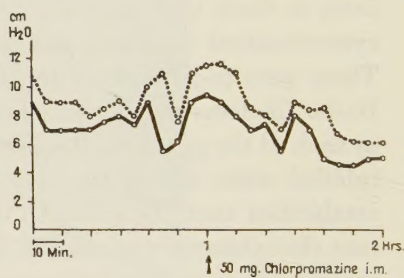


Fig. 3. Dog II.

Dog II (fig. 3). The second dog, also weighing 16 kg., had a normotensive sphincter resistance during the first hour of the test. When 50 mg. of chlorpromazine were administered intramuscularly at the end of that hour a decrease in pressures showed that the sphincter had dilated slightly in response to the drug.

Dog III (fig. 4). This dog, which weighed 17 kg., had a markedly hypertensive sphincter. Twenty minutes after the onset of testing 170 mg. of chlorpromazine were injected intravenously over a period of twenty minutes. During the time of the injection and in the following fifteen minutes pressures rose. Then a marked decrease in resistance was recorded and the pressure values remained level during the next hour.

Dog IV (fig. 5). This fourth dog weighing 24 kg. was injected with 240 mg. of chlorpromazine intravenously over a period of twenty minutes after the first hour of readings showed a normotensive sphincter. During fifteen of those twenty minutes pressures rose slightly. A minimal decrease in resistance followed and during the next hour and a half no appreciable changes in pressures were recordable.

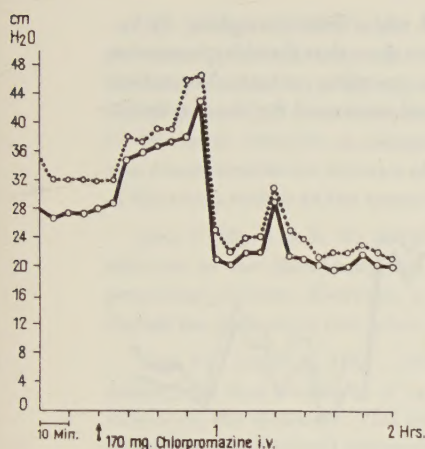


Fig. 4. Dog III.

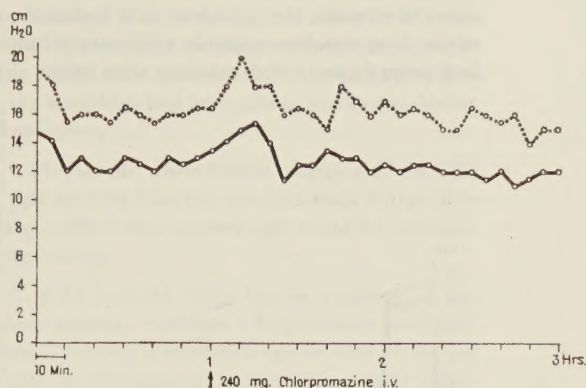


Fig. 5. Dog IV.

Patients

Case I (fig. 6). E. H., 25 860-56, a 55-year-old white female weighing 62 kg. The accompanying curve shows that during the hour preceding the intramuscular injection of 25 mg. of chlorpromazine, normotensive levels existed. The drug was injected sixty minutes after the test began, and during the next fifty minutes sphincter resistance gradually decreased. Hypotensive pressure readings were recorded for the following four hours, and at the end of that time the test was concluded.

Case II (fig. 7). E. B., 25 214-56, a 55-year-old white female weighing 58 kg. The four pressure readings taken before chlorpromazine administration were within normal range. Immediately after the fourth reading the test dose was administered. Ten minutes thereafter no appreciable change had occurred, but the following reading showed that a very rapid decrease in resistance had taken place. An extreme degree of dilation was maintained for two hours. The recovery period ensued, and four and a half hours after injection of the drug the norm had again been reached.

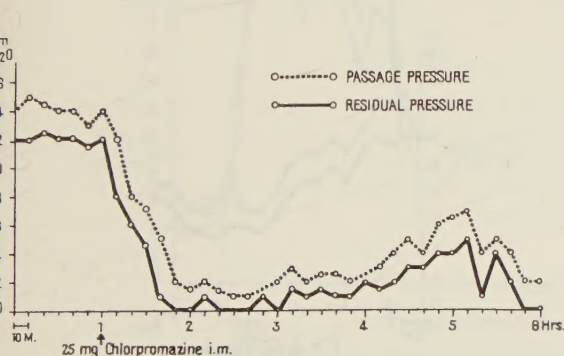


Fig. 6. Case I.

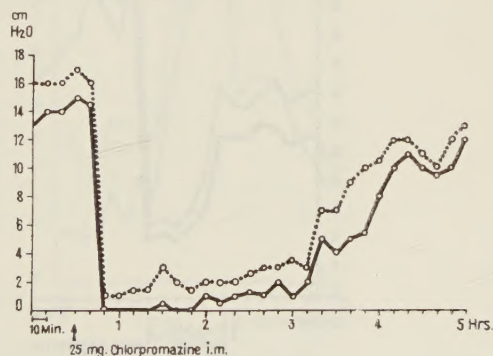


Fig. 7. Case II.

Case III (fig. 8). M. T., 29953-56, a 60-year-old white female weighing 75 kg. The graphic depiction of the test results for this patient show that the chlorpromazine acted in virtually the same way as it had in the two preceding patients. The action of the drug was demonstrable within ten minutes and continued for the two and a half hours during which readings were taken.

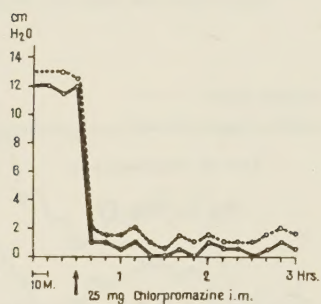


Fig. 8. Case III.

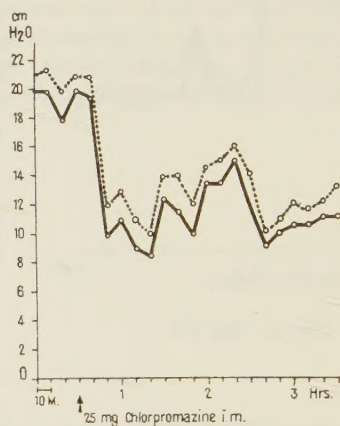


Fig. 9. Case IV.

Case IV (fig. 9). M. S., 31947-56, a 50-year-old white female weighing 51 kg. Preinjection pressure values for this patient were hypertensive. This caused speculation as to what the response of the sphincter would be when a state of hypertonicity existed. Once again the chlorpromazine acted to dilate the sphincter. The normotensive condition which followed was maintained for the next three hours.

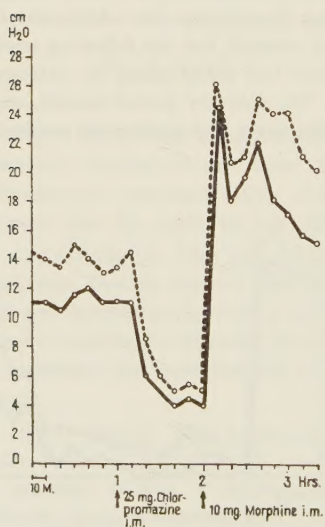


Fig. 10. Case V.

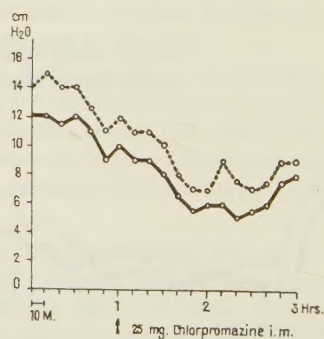


Fig. 11. Case VI.

Case V (fig. 10). F. W., 538-57, a 59-year-old white female weighing 53 kg. The pressures in the hour before the chlorpromazine injection were normotensive. During the sixty minutes after injection the sphincter showed the typical effect. When this effect had reached its maximum, 10 mg. of morphine were injected intramuscularly to determine whether an antagonistic effect could be achieved. A sphincter spasm was demonstrable ten minutes after the morphine had been given. At the conclusion of the test a return to the norm was underway.

Case VI (fig. 11). R. B., 2537-57, a 24-year-old white female weighing 65 kg. The reaction to the chlorpromazine in this patient was less marked than in the five preceding patients. However, a dilatory effect was present and could be recorded during the remaining two hours of the testing.

Case VII (fig. 12). H. F., 4014-57, a 43-year-old white female weighing 65 kg. During the first half hour of recording pressure readings a hypotensive condition existed at the sphincter. This suggested inducing a morphine spasm with 10 mg. of morphine administered intramuscularly to subsequently better demonstrate chlorpromazine's dilatory effect. Sphincter resistance increased rapidly and reached a peak within thirty minutes. In the next ninety minutes values, though high, tended to level off. Chlorpromazine was then injected. Ten minutes thereafter a substantial decrease in pressures had taken place. The sphincter continued to dilate and in the last eighty minutes pressure values reached a plateau approximately equal to that at the onset of testing.

Case VIII (fig. 13). W. M., 4575-57, a 39-year-old white male weighing 71 kg. In the hour preceding the injection of a test dose the readings were slightly hypo-



Fig. 12. Case VII.

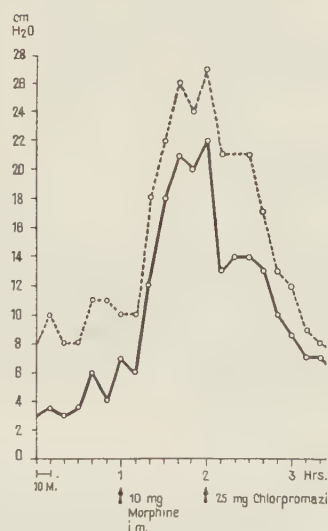


Fig. 13. Case VIII.

tensive and inconstant. At the end of that time it was decided that a morphine-induced spasm would more clearly demonstrate the chlorpromazine effect than an initial injection of the chlorpromazine. The rise in pressures during the next hour demonstrated the action of the morphine on the sphincter, and when resistance was maximal chlorpromazine was given. The antagonistic action of the latter drug to the morphine began almost immediately. The dilatory effect of the chlorpromazine within the next hour and a half returned the pressure values to those initially recorded.

Case IX (fig. 14). L. S., 3123-57, a 44-year-old white female weighing 50 kg. This patient's pressure values were hypotensive at the onset of the testing. When chlorpromazine was injected a slight response was noted, although the effect was minimal. A morphine-induced spasm was contraindicated because the patient had previously displayed a sensitivity to the drug.

Case X (fig. 15). A. H., 5640-57, a 45-year-old white male weighing 54 kg. This patient also reacted to the chlorpromazine with a decrease in pressures. The effect was evident within twenty minutes and was maintained for two hours, at which time the test was concluded.

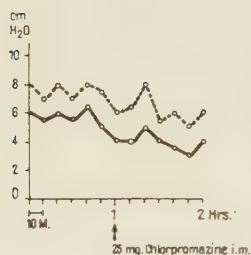


Fig. 14. Case IX.

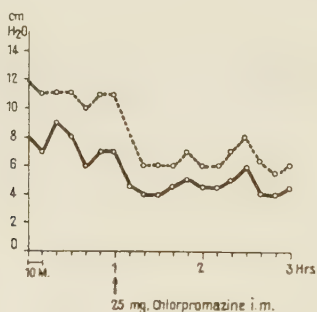


Fig. 15. Case X.



Fig. 16. Case XI.

Case XI (fig. 16). H. S., 6633-57, a 29-year-old white female weighing 74 kg. During the first hour of testing this patient maintained constant but hypotensive values, and therefore was given morphine. The sphincter spasm, which rapidly ensued, was counteracted by chlorpromazine when a peak level had been reached thirty minutes later. Within a half hour chlorpromazine had dilated the sphincter sufficiently to return pressure levels to a normal range.

Discussion

Dogs

The test results obtained from the four dogs demonstrate that we are unable to report findings coinciding with those of the investigators

at the Mayo Clinic. Dog I and II, receiving 50 mg. of chlorpromazine intramuscularly, responded with decreases in passage and residual pressures. Dog III during and immediately after the intravenous injection of 170 mg. of the drug reacted with an increased resistance, but as this was followed by a marked decrease in pressures we suspect that the initial rise was the expression of an autonomic nervous system response to the sizable dose. This assumption seems justified since it is not typical of the drug in high doses to elicit responses of only short duration. Dog IV also reacted to 240 mg. of chlorpromazine intravenously administered with an increase in pressures during the time of injection. A slight decrease in resistance followed indicating that the same mechanism was involved as we described for Dog III.

Patients

The most significant passage pressure and residual pressure values obtained from the eleven patients are summarized in the accompanying table (fig. 17). It should be noted that of the eight patients receiving an initial dose of chlorpromazine between thirty and sixty minutes after testing began, four responded with a rapid and marked

Results: Passage pressure/Residual pressure

	Preinjection levels	Chlorpromazine minimal levels	Morphine maximal levels	Chlorpromazine minimal levels	Changes in sphincter resistance
1.	14.0/12.0	1.5/0.0			—12.5/—12.0
2.	17.0/15.0	1.0/0.0			—16.0/—15.0
3.	12.5/12.0	1.5/0.5			—11.0/—11.5
4.	21.0/19.5	10.0/8.5			—11.0/—11.0
5.	13.5/11.0	5.0/4.0	26.0/25.0		— 8.5/— 7.0 +21.0/+21.0
6.	12.0/10.0	7.0/5.5			— 5.0/— 4.5
7.	6.0/ 4.0		31.0/28.0	9.0/7.0	+25.0/+24.0 —22.0/—21.0
8.	10.0/ 7.0		27.0/22.0	7.5/6.0	+17.0/+15.0 —19.5/—16.0
9.	6.0/ 4.0	5.0/3.0			— 1.0/— 1.0
10.	11.0/ 7.0	6.0/4.0			— 5.0/— 3.0
11.	6.0/ 4.0		19.0/17.5	9.5/8.0	+13.0/+13.5 — 9.5/— 9.5

Fig. 17

decrease in pressures (between -11.0 and -16.0), three with a moderate decrease (between -5.0 and -8.5), and one with a very slight decrease (-1.0). The fifth of those eight patients was injected with morphine after the chlorpromazine and reacted with a substantial increase in pressures ($+21.0$) demonstrating a morphine-induced spasm. The three remaining patients were given morphine prior to chlorpromazine. Each of the three responded with a marked increase in pressures after morphine (between $+13.0$ and $+25.0$), and a marked decrease after chlorpromazine (between -9.5 and -22.0). None of the eleven patients tested showed an increase in resistance at the sphincter of Oddi after chlorpromazine administration.

Summary

The results of this study show that in man a single dose of 25 mg. of chlorpromazine injected intramuscularly acts on the choledochoduodenal sphincter within ten to twenty minutes causing a dilation of this sphincter as demonstrated by the measurable decrease in passage pressures and residual pressures using the Caroli apparatus and method. Further, that morphine injected intramuscularly in a single dose of 10 mg. initiates a biliary sphincter spasm, and that such a morphine-induced spasm can be relieved by the subsequent injection of 25 mg. of chlorpromazine demonstrating the effectivity of the latter drug when resistance at the sphincter is high.

We conclude from this investigation that at present the chlorpromazine jaundice with stasis in the biliary tree can not be attributed to the direct effect of the drug on the choledochoduodenal sphincter.

It remains to be determined whether prolonged administration of chlorpromazine might alter the typical reaction of the sphincter.

Further studies regarding the advisability of using chlorpromazine as an antispasmodic to relieve biliary colic, where liver function tests show that there is no contra-indication to such use, are suggested. Preliminary investigation on two patients with biliary colic resulting from cholelithiasis indicates that symptoms can be relieved in ten to twenty minutes for periods of two to three hours with doses of 25 mg. administered intramuscularly.

Zusammenfassung

Eine einmalige Dosis von 25 mg Chlorpromazin i.m. führt innert 20 Minuten zu einer Erweiterung des Choledochoduodenalsphinkters,

d. h. zu einem Abfall des Passage- und Residualdruckes. Der durch eine einmalige Dosis von 10 mg Morphin ausgelöste Sphinkterspasmus wird durch eine nachfolgende Dosis von 25 mg Chlorpromazin gelöst; diese ist also auch bei erhöhter Sphinkterresistenz wirksam.

Daraus kann geschlossen werden, daß der Chlorpromazin-Ikterus mit Cholestase in den Hepaticusverzweigungen nicht auf einer direkten Wirkung des Mittels auf den choledochoduodenalen Sphinkter beruht. Es ist zu untersuchen, ob wiederholte Applikation zu einer Änderung der Sphinkterreaktion führt. Es wird angeregt, die Verwendbarkeit des Chlorpromazins als Antispasmodikum bei Gallenkolik zu prüfen bei Fällen, bei welchen die Leberfunktionsteste keine Kontra-indikation ergeben. Bei zwei Patienten mit Koliken bei Cholelithiasis wurde innert 10–20 Minuten während 2–3 Stunden mittels 25 mg Chlorpromazin Schmerzfreiheit erzielt.

Résumé

Expérimentalement, une dose unique de 25 mg. de chlorpromazine chez le chien, produit en 20 minutes un relâchement du sphincter d'Oddi, avec chute des pressions de passage et résiduelle. Le spasme provoqué par 10 mg. de morphine est inhibé par une dose subséquente de 25 mg. de chlorpromazine: celle-ci est donc efficace également en clinique, dans les cas de résistance oddienne augmentée.

On peut tirer de ces recherches expérimentales que l'ictère de la chlorpromazine avec cholestase dans les branches du canal hépatique, ne provient pas d'une action directe du médicament sur le sphincter cholédoco-duodéal. Il faudrait cependant étudier si une administration répétée n'entraînerait pas un autre genre de réaction sphinctérienne. Il serait intéressant de contrôler l'efficacité antispasmodique de la chlorpromazine dans des coliques biliaires (quand les épreuves fonctionnelles hépatiques ne le contre-indiquent pas); dans deux cas de lithiase cholédocienne, les coliques cédèrent en 10 à 20 minutes, et pour 2 à 3 heures, à 25 mg. de chlorpromazine.

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Curriculum Vitae

I was born on July 7, 1930, in Homburg, Saar, and in 1935 emigrated to the United States of America of which I have been a citizen since 1941. My formal education took place at the following schools and universities: Public Schools 90 and 114 in The Bronx, New York; Wm. J. Taft High School, The Bronx, New York (Academic Diploma, June 1948); Syracuse University, Syracuse, New York (Bachelor of Arts Degree, June 1952); Basel University, Basel, Switzerland (Anatomisch-physiologische Prüfung, March 22, 1955).

At present I plan to take the Swiss State Board Examination for the Degree of Doctor of Medicine in August of 1958. Upon successful completion of the examination I shall return to New York to continue my studies at Lebanon Hospital, The Bronx, New York, where I have obtained an internship.